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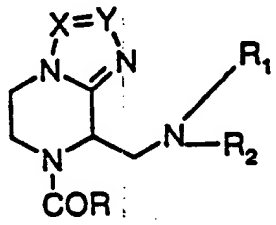
(57) Abstract



(I)

Azacyclic derivatives of formula (I) in which each of X and Y is independently CH or N; RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring; each of R_1 and R_2, which may be the same or different, is C_{1-6} alkyl optionally substituted by at least one of halogen, hydroxy, C_{1-6} alkoxy, acyloxy, thiol, C_{1-6} alkylthio, alcylthio, halo-C_{1-6} alkoxy, COR_h, $COOR_h$, $CONHR_h$ or $NCHOR_h$ where R_h is hydrogen or C_{1-6} alkyl; or each of R_1 and R_2 is hydrogen, C_{2-6} alkenyl, C_{3-6} cycloalkyl, or C_{4-12} cycloalkylalkyl; or R_1 and R_2 together form an optionally substituted C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, are kappa-receptor agonists and are useful in the treatment of pain, convulsions, cough, asthma, inflammation, pancreatitits, arrhythmias, hyponatraemic disease states, cerebral ischaemia or skin disorders.

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AZACYCLIC DERIVATIVES

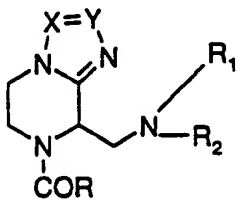
This invention is concerned with novel substituted azacyclic condensed piperazines, processes for their preparation, and their use in medicine, particularly as diuretics and anti-ischaemics.

Compounds which are kappa receptor agonists have mainly been studied as analgesics through interaction with kappa opioid receptors. The advantage of kappa receptor agonists over the classical mu receptor agonists, such as morphine, lies in their ability to cause analgesia while being devoid of morphine-like behavioural effects and addiction liability.

EP-A-343900 and EP-A-398720 (Glaxo Group Ltd.), and EP-A-356247 (Sankyo Co. Ltd.) disclose groups of piperazine derivatives which are said to exhibit kappa receptor agonism and are therefore said to be useful as analgesics, as diuretics and in the treatment of cerebral ischaemia.

A novel class of structurally related azacyclic condensed piperazine derivatives has now been discovered which also exhibit potent kappa receptor agonism and are particularly useful as diuretics for the treatment of hyponatraemic disease states in mammals and anti-ischaemics, in particular for the treatment of cerebral ischaemia. This novel class of derivatives also possess analgesic activity which indicates that they are of potential use in the treatment of pain, without some of the undesirable behavioural effects of morphine and morphine analogues. The novel class of derivatives are also of potential use in the treatment of other conditions which respond to administration of kappa agonists, in particular convulsions, cough, asthma, inflammation (including inflammation pain), pancreatitis, arrhythmia's and skin disorders.

According to the present invention there is provided a compound, or a solvate or salt thereof, of formula (I):



(I)

in which:

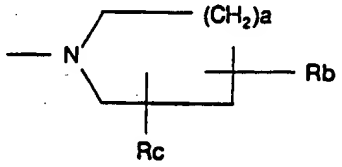
each of X and Y is independently CH or N;

RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

each of R_1 and R_2, which may be the same or different, is C_{1-6} alkyl optionally substituted by at least one of halogen, (preferably fluorine or chlorine), hydroxy, C_{1-6} alkoxy (preferably methoxy), acyloxy (preferably acetoxy), thiol, C_{1-6} alkylthio (preferably methylthio), acylthio (preferably acetylthio) halo-C_{1-6} alkoxy (preferably fluoro-alkoxy), COR_h, $COOR_h$, $CONHR_h$ or $NHCOR_h$ where R_h is hydrogen or C_{1-6} alkyl, preferably methyl or ethyl;

or each of R_1 and R_2 is hydrogen, C_{2-6} alkenyl, C_{3-6} cycloalkyl, or C_{4-12} cycloalkylalkyl;

or R_1 and R_2 together form an optionally substituted C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, the polymethylene group, with the attached nitrogen, preferably being of the formula



in which Rb, which may be attached to the same or different carbon atom as Rc, is hydrogen, hydroxy, C_{1-6} alkoxy (preferably methoxy) or halogen (preferably fluorine), and Rc is hydrogen, C_{1-6} alkyl (preferably methyl) or together with Rb forms a keto-group or a cyclic ether containing from 1 to 4 carbon atoms, and a is 1 or 2.

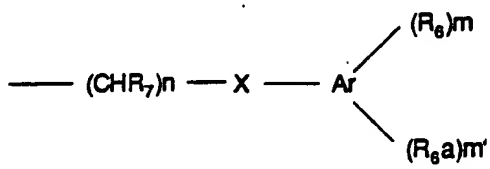
Examples of NR_1R_2 are 1-pyrrolidinyl, 3-hydroxy-1-pyrrolidinyl and 3-fluoro-1-pyrrolidinyl.

When used herein to define the RCO group, the term 'carbocyclic aromatic group' includes single or fused rings, having 6 to 12 ring carbon atoms, and the term 'heterocyclic aromatic group' includes single or fused rings having 5 to 12 ring atoms, comprising up to four hetero-atoms in the or each ring, selected from oxygen, nitrogen and sulphur.

When the carbocyclic or heterocyclic group is a fused two ring system, one or both rings may be aromatic in character.

Suitably, one of the rings is aromatic and the other is non-aromatic.

The group R preferably has the formula (II):



(II)

in which n is 0, 1 or 2;

m is 0, 1 or 2;

m' is 0, 1 or 2, provided m + m'≤3

X is a direct bond, or O, S or NR_8 in which

R_8 is hydrogen or C_{1-6} alkyl,

Ar is a substituted or unsubstituted carbocyclic or heterocyclic group,

each of R_6 and R_6a is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkenyl, C_{2-6} haloalkynyl, optionally substituted phenyl or heterocyclyl, optionally substituted phenyl C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, thiol, C_{1-6} alkylthio, C_{1-6} haloalkoxy, C_{1-6} haloalkylthio, halogen, NO_2, CN, CF_3, $-OCF_3$, $-OCHF_2$, $-OCF_2CF_2H$, $-OCCl_2CF_3$, $-COOR_9$, $-CONR_{10}R_{11}$, $-SO_3R_{12}$, $-SO_2NR_{13}R_{14}$ and $-COR_{15}$ in which each of R_9 to R_{15} is independently hydrogen, C_{1-6} alkyl, optionally substituted phenyl or optionally substituted phenyl C_{1-6} alkyl;

or, when m is 2 and m' is 0, two R_6's form a C_{3-6} polymethylene group,

and R_7 is hydrogen or C_{1-6} alkyl, such as methyl or ethyl.

When R_6 or R_6a is heterocyclyl, it is preferably an aromatic or non-aromatic single or fused ring system having from 5 to 12 ring atoms, comprising up to 4 hetero-atoms in the or each ring, selected from oxygen, nitrogen and sulphur.

Preferred halogens are F, Cl and Br.

When two R_6's are linked they preferably form a fused cyclopentyl or cyclohexyl ring.

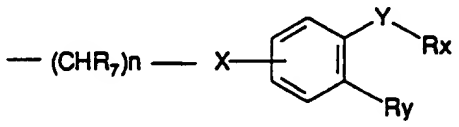
Preferably Ar is phenyl and R_6 or R_6^a is preferably in the meta- and/or para-position.

Other examples of Ar are naphthyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indolyl, 2,3-dihydrobenzopiranyl and 2,3-dihydrobenzothio piranyl.

Preferably R_6 or R_6a is bromine, chlorine, CF_3, 2-furanyl, 2-pyrryl, 2-thiazolyl, 2-imidazolyl or 2-thienyl, particularly, when Ar is phenyl, in the meta and/or para position.

X is typically oxygen or a direct bond, and n is typically 0 or 1.

A further preferred group R has the formula (IIa)

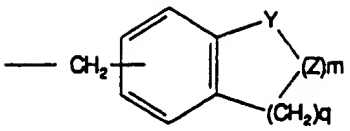


(IIa)

in which the group $-(CHR_7)_n-X-$, which is as defined in formula II, is in the meta- or para- position with respect to YR_x or R_y,

Y is >C=O, >CHOH, >S=O or $>SO_2$;
each of R_x and R_y is C_{1-6} alkyl, or
R_x and R_y are linked together and R_x represents $-(Z_m)-$
where m is 0 or 1 and Z is O, S or NR_z where R_z is hydrogen or C_{1-6} alkyl,
and R_y represents $-(CH_2)_q-$ where q is an integer of from 1 to 4, preferably 2 or 3.

A preferred sub-group of formula (IIa) is a group of formula (IIb)

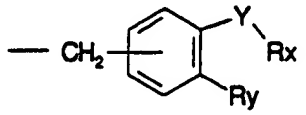


(IIb)

in which Y, Z, m, q and the position of -CH_2- are as defined in formula (IIa).

Preferably, q is 2 when Z is oxygen and m is 1, and q is 3 when m is 0.

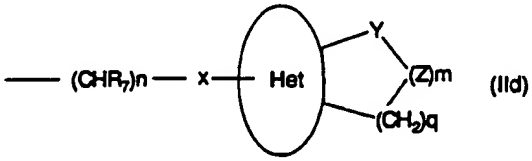
A further preferred sub-group of formula (IIa) is the group of formula (IIc)



(IIc)

in which Y is C=O or CHOH, each of R_x and R_y is C_{1-6} alkyl, preferably methyl, and the position of -CH_2- is as defined in formula (IIa)

A further preferred group R has the formula (IId)



(IId)

where Het is the remainder of a single aromatic heterocyclic ring, containing from 5 to 6 ring atoms and comprising up to 3 heteroatoms in the ring selected from O, S and N;
and R_7, X, Y, Z, m and q are as defined in formula (IIa)

Particularly preferred examples of R are 3,4-dichlorobenzyl or 4-trifluoromethylbenzyl.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

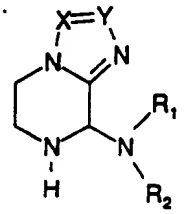
One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of a pharmaceutically acceptable salt of a compound of formula (I) include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicyclic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Examples of a pharmaceutically acceptable solvate of a compound of formula (I) include the hydrate.

The compounds of formula (I) have at least one asymmetric centre and therefore exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including racemates.

The present invention also provides a process for the preparation of a compound of formula (I) which comprises treating a compound of formula (III)



(III)

in which R_1, R_2, X and Y are as defined in formula (I), with a compound of formula RCOOH, or an active derivative thereof, and optionally thereafter forming a salt and/or solvate of the obtained compound of formula (I).

Suitable active derivatives of RCOOH are acid chlorides or acid anhydrides. Another suitable derivative is a mixed anhydride formed between the acid and an alkyl chloroformate.

For example, in standard methods well known to those skilled in the art, the compound of formula (III) may be coupled:

a) with an acid chloride in the presence of an inorganic or organic base in an aprotic solvent such as dichloromethane or dimethylformamide,

b) with the acid in the presence of dicyclohexyl carbodiimide or carbonyl diimidazole,

c) with a mixed anhydride generated in situ from the acid and an alkyl (for example isobutyl) chloroformate.

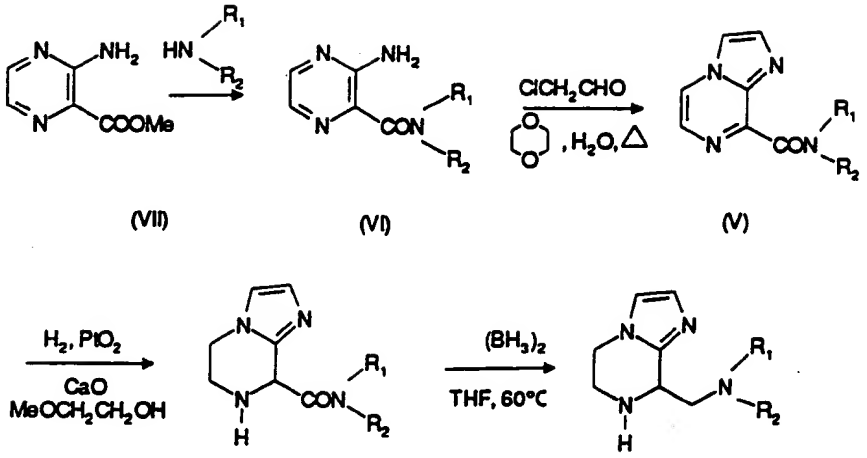
The compounds of formula (I)may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids. Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example hydrates may be formed by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

As mentioned before, the compounds of formula (I) exist in more than one stereoisomeric form and the process of the invention produces mixtures thereof. The individual isomers may be separated one from another by resolution using an optically active acid such as tartaric acid. Alternatively, an asymmetric synthesis would offer a route to the individual form.

Compounds of formula (III) may themselves be prepared from known compounds by known methods. For example, compounds in which both X and Y are -CH- (formula (IIIa) may be prepared by the following reaction Scheme I:

Scheme I



In this scheme, a compound of formula (VI) is prepared from the known compound (VII) (J. Am. Chem. Soc. 1945, 67, 1711) by reaction with an excess of the appropriate amine in the absence or presence of solvent such as MeOH.

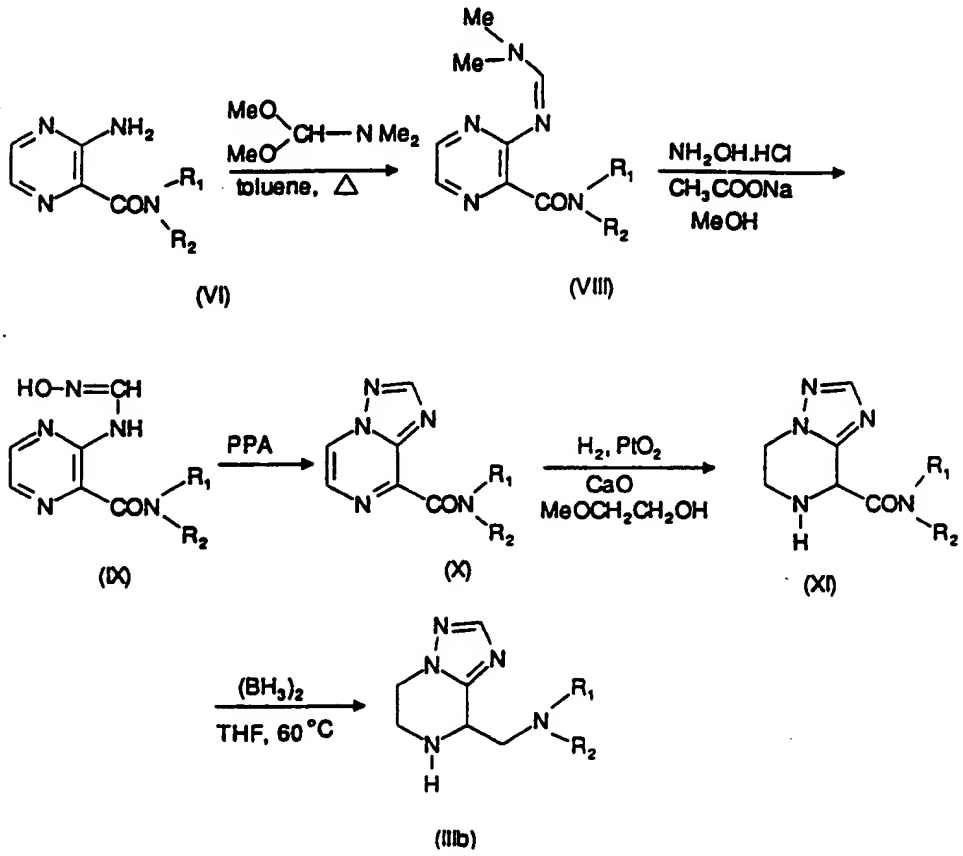
Compound (VI) is thereafter treated with a haloacetaldehyde such as chloro acetaldehyde or bromoacetaldehyde in a dioxane/water mixture at a temperature of 90°C for a prolonged period of time (from 8 to 48 hours), and the resulting compound of formula (V) is hydrogenated over a suitable catalyst such as PtO2 or 5% Pt/C in the presence of calcium oxide in an appropriate solvent such as ethanol or 2-methoxyethanol.

Reduction of the compound (IV) with diborane or borane methyl sulfide complex in refluxing THF affords the desired compound of formula (IIIa).

The intermediates of formulae (V), (IV) and (IIIa) and salts and solvates thereof, are novel compounds and, as such, they form a further aspect of this invention.

Compounds of formula III in which X is -N- and Y is -CH- (formula (IIIb)) may be prepared according to the following reaction Scheme II

Scheme II



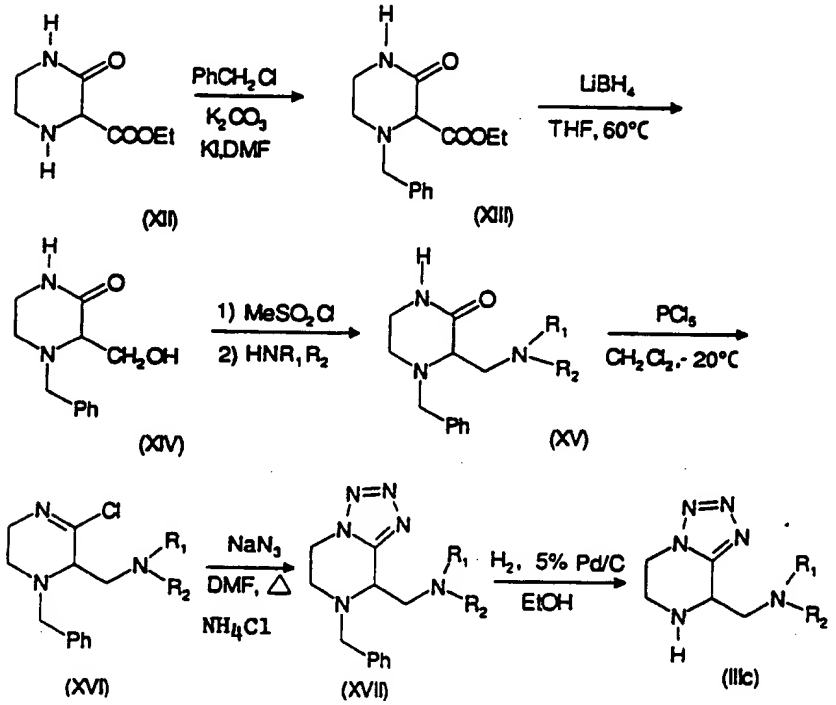
In this scheme, the compound of formula (VI) is treated with an excess of N,N-dimethylformamide dimethyl acetal in refluxing toluene to obtain a compound of formula (VIII). Displacement of the N,N-dimethylamino group with the oxime group in MeOH as solvent gives a compound of formula (IX), which is then cyclized in polyphosphoric acid at a temperature of 80-100°C.

The resulting compound of formula (X) is hydrogenated over a suitable catalyst, such as PtO_2 or 5% Pt/C in the presence of calcium oxide in an appropriate solvent such as ethanol or 2-methoxyethanol to obtain a compound of formula (XI). Reduction of this with diborane or borane methyl sulfide in refluxing THF affords the desired compound of formula (IIIb)

The intermediates of formulae (VIII), (IX), (X), (XI) and (IIIb) and salts and solvates thereof, are novel compounds and, as such, they form a further aspect of this invention.

Compounds of formula (III) in which both X and Y are -N- (formula (IIIc) may be prepared according to the following reaction Scheme III.

Scheme III



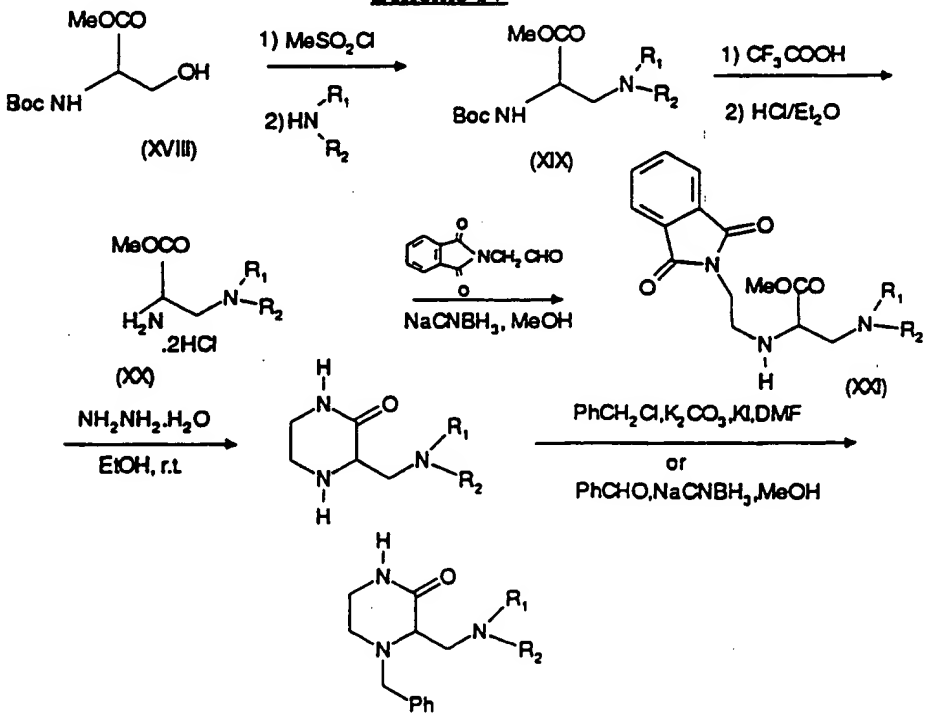
In this scheme, the known compound of formula (XII) (U.S. Patent 4,578,378) is N-protected with an alkylation procedure and the resulting compound of formula

(XIII) is treated with a selective reductive agent such as lithium borohydride in refluxing THF to obtain the compound of formula (XIV). This intermediate is activated with methanesulphonyl chloride or p-toluene sulphonyl chloride in dichloromethane as solvent and subsequently treated with the appropriate amine. The resulting compound of formula (XV) is transformed into the corresponding imidoyl chloride by treatment with PCl_5 in dichloromethane.

Intermediate (XVI) is thereafter submitted to a 1,3-dipolar cycloaddition reaction with sodium azide and ammonium chloride in refluxing DMF to obtain a compound of general formula (XVII) which may be deprotected by using hydrogen over 5% Pd/C as catalyst in a suitable solvent such as ethanol or methanol, affording the desired compound of formula (IIIc).

Alternatively, compounds of formula (XV) may be prepared by an intramolecular cyclization according to Scheme IV:

Scheme IV



In this Scheme , the known compound of formula (XVIII) (CAS[69942-12-7], Angew. Chem., Int. Ed. Engl., 11, 289 (1972)) is activated by treatment with

methanesulphonyl chloride or p-toluenesulphonyl chloride in a suitable solvent such as dichloromethane and then treated with the appropriate amine. The resulting compound (XIX) is thereafter deprotected by using trifluoroacetic acid and directly transformed into the dihydrochloride salt by treatment with HCl/Et_2O.

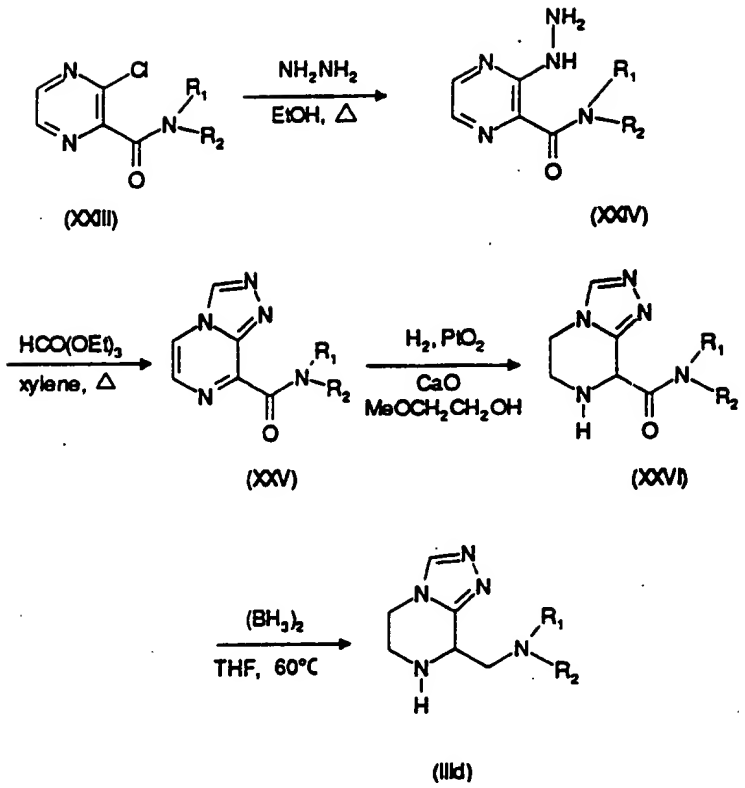
The compound of formula (XX) is submitted to a reductive amination procedure with phthalimido acetaldehyde in the presence of an alkali metal hydride such as $NaBH_4$ or $NaCNBH_3$ in a suitable alchoholic solvent.

The resulting compound of formula (XXI) is thereafter cyclized intramolecularly by treatment with hydrazine hydrate in ethanol at room temperature to obtain a compound of formula (XXII).

A direct alkylation with benzyl chloride in the presence of K_2CO_3 and KI or with benzaldehyde in the presence of $NaCNBH_3$ in MeOH gives the desired compound of formula (XV).

Compounds of formula (III) in which X is -CH- and Y is -N- (formula (IIId) may be prepared according to the following reaction Scheme (V).

Scheme V



(XXIII) (XXIV) (XXV) (XXVI) (IIId)

In this scheme, a compound of formula (XXIII) is treated with hydrazine in refluxing ethanol and the resulting compound of formula (XXIV) is thereafter cyclized with triethyl orthoformate in refluxing xylene.

The obtained compound of formula (XXV) is selectively reduced by hydrogenation over PtO_2 in the presence of calcium oxide in a suitable solvent such as 2-methoxyethanol to obtain a compound of formula (XXVI).

Reduction of this with diborane or borane methyl sulfide complex in refluxing THF affords the desired compound of formula (IIId).

The compound of general formula (XXIII) can be obtained from a known compound using known methods, for example as described in J. Heterocycl. Chem. 1979, 16(1), 193-4 and in Heterocycles 1984, 22 (2), 299-301.

The activity of the compounds of formula (I) in standard tests indicates that they are of potential therapeutic utility in the treatment of pain, cerebral ischaemia, hyponatraemic disease states, convulsions, cough, asthma, inflammation (including inflammation pain) pancreatitis, arrythmias and skin disorders (hereinafter referred to as the Conditions).

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, (hereinafter referred to as the Compounds) in the manufacture of a medicament for the treatment of the Conditions.

The present invention also provides a method for the treatment and/or prophylaxis of the Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of the Compound.

Medicaments and compositions containing the Compounds may be prepared by admixture of a Compound with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for the treatment of the Conditions.

Preferably, a medicament or pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent for the treatment of each of the Conditions.

The suitable dosage range for a Compound depends on the Compound to be employed, the Condition to be treated, and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The Compound may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may b presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid

compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The Compounds may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example, for rectal administration as a suppository or for topical administration as a cream or lotion. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The Compounds may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a Compound and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised Compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the Compound particle size is from about 2 to 10 microns.

A further mode of administration of the Compounds comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a Compound dispersed in a pressure sensitive adhesive which adheres to the skin,

thereby permitting the Compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

The effective dose of Compound depends on the particular Compound employed, the Condition to be treated, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected when the Compounds are administered in accordance with the invention.

The kappa receptor affinity of the Compounds may be demonstrated by in vitro binding experiments using a kappa selective radioligand (Sbacchi et al., Excerpta Medica, Vol. 914,211-212, 1990).

The diuretic activity of the compounds may be evaluated by measuring the urine volume in normally hydrated or water loaded rats, in agreement with the methods described by J .D. Leander, J. Pharmacol. Exp. Ther., 1983, Vol. 224, 89 and by A.G. Hayes, J. Pharmacol. Exp., 1987, Vol. 240, 984.

The activity of the Compounds in treating cerebral ischaemia may be evaluated by using the gerbil model of ischaemic stroke, as described by P. Lysko et al., Stroke, 1992, Vol. 23(3).

The analgesic activity of the Compounds may be demonstrated using the p-phenylquinone-induced abdominal constriction test in mice (Siegmund et al, Proc. Soc. Exp. Biol. 95, 729-, 1957, modified by Milne and Twomey, Agents and Actions, 10, 31-, 1980).

The effects of the Compounds in protecting against inflammation pain may be demonstrated using the paw pressure test in the monoarthritic rat as described in Eur. J. Pharmacol. 155, 255-264, 1988. Following subcutaneous administration, the Compounds produce an enhanced analgesic effect in the inflamed paw compared to the non-inflamed paw. The analgesic effect in the inflamed paw is completely reversed by a low intraplantar dose of the opioid antagonist, naloxone, but not by a similar dose of naloxone administered subcutaneously.

Further evidence for the peripheral analgesic action of Compounds may be obtained by a modification of the abdominal constriction test as described in Br. J. Pharmacol. 73, 325-332, 1981. After administration of PPQ or acetylcholine, intraperitoneal administration of the Compounds produce a decrease in the number of abdominal constrictions.

Compounds of this invention and their preparation are illustrated in the following Examples, and their structures are summarised in the Table.

The preparation of intermediates is illustrated in the Descriptions.

Description 1

3-Amino-2-(1-pyrrolidinylcarbonyl)pyrazine

A mixture of 10 g (0.065 moles) of 3-Aminopyrazine-2-carboxylic acid methyl ester and 150 ml of pyrrolidine was stirred three days at room temperature.
The excess of pyrrolidine was evaporated in vacuo and the residue crystallized from ethyl acetate/n-hexane to yield 8.65 g of the title compound.

$C_9H_{12}N_4O$

M.P. = 102-103°C
M.W. = 192.218

N.M.R. (80 MHz) : δ 8.05 (d,1H), 7.80 (d,1H), 6.60 (s, broad,2H), $CDCl_3$ 3.55-3.95 (m,4H), 1.80-2.05 (m,4H).

Analogously, 3-Amino-2-[(3-hydroxy-1-pyrrolidinyl)carbonyl]pyrazine was prepared.

Description 2

8-(1-Pyrrolidinylcarbonyl)-imidazo[1,2-a]pyrazine

A mixture of 8.64 g (0.045 moles) of 3-Amino-2-(1-pyrrolidinyl-carbonyl)pyrazine and 8.7 ml (0.067 moles) of 50% chloro-acetaldehyde (water) was heated at 100°C for 2 days in the presence of 5.6 g (0.067 moles) of sodium bicarbonate.
The reaction mixture was then evaporated in vacuo to dryness and the residue, treated with acqueous potassium carbonate, was exhaustively extracted with dichloromethane. The organic solution was evaporated in vacuo to dryness and the crude product purified by silica gel flash column chromatography , eluting with a mixture of CH_2Cl_2/MeOH/28% NH_4OH, 95:5:0.5 respectively, to obtain 2.2 g of the title compound.

$C_{11}H_{12}N_4O$

M.P. = 154-156°C
M.W. = 216.238

I.R. (film) : 3130; 2980; 2880; 1635; 1425; 1320 cm^{-1}

N.M.R. (80 MHz): δ 8.25 (d,1H), 7.75-7.95 (m,3H), 3.80 (t,2H), $CDCl_3$ 3.35 (t,2H), 1.80-2.10 (m,4H).

Analogously, 8-[(3-hydroxy-1-pyrrolidinyl)carbonyl]-imidazo[1,2-a]pyrazine was prepared.

Description 3

8-(1-Pyrrolidinylcarbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine

2.10 g (9.58 mmoles) of 8-(1-pyrrolidinylcarbonyl)-imidazo[1,2-a]pyrazine, dissolved in 30 ml of 2-methoxyethanol were hydrogenated in a Parr apparatus over 190 mg of PtO_2 in the presence of 580 mg of powdered calcium oxide. After the theoretical amount of hydrogen was consumed, the catalyst was filtered off and the filtrate evaporated in vacuo to dryness to yield 2.1 g of the title compound as an orange oil.

$C_{11}H_{16}N_4O$

M.W. = 220.270

N.M.R. (80 MHz) :δ 6.98 (d,1H), 6.80 (d,1H), 5.00 (s, 1H), 3.85-$CDCl_3$ 4.35 (m,3H), 2.70-3.65 (m,6H), 1.70-2.10 (m,4H).

Analogously, 8-[(3-hydroxy-1-pyrrolidinyl)carbonyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine diastereomeric mixture was prepared.

Description 4

8-(1-Pyrrolidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine

2.1 g (9.53 mmoles) of 8-(1-pyrrolidinylcarbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine were dissolved in 60 ml of dry THF. The solution was warmed to 60°C and 2.8 ml of a 10 M solution of borane dimethylsulfide complex were added dropwise under nitrogen and mechanical stirring.

The reaction mixture was allowed to reflux for 6 hours, cooled to -10°C, carefully treated with 6N HCl and warmed again for 3 hours at 70°C.
The solvent was then evaporated in vacuo to dryness and the residue treated with 40% acq. NaOH solution. The crude diamine was exhaustively extracted with CH_2Cl_2, which was dried over Na_2SO_4 and concentrated in vacuo to dryness to yield 2.0 g of the title compound with a purity of 88% (GC). The compound was used without further purification in the subsequent reaction.

$C_{11}H_{18}N_4$

M.W. = 206.286

N.M.R. (80 MHz) : $CDCl_3$ δ 7.00 (d,1H), 6.82 (d,1H), 2.40-4.20 (m,12H), 1.65-1.85 (m,4H).

Analogously, 8-[(3-Hydroxy-1-pyrrolidinyl)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine diastereomeric mixture was prepared.

Description 5

3-Dimethylaminomethyleneamino-2-(1-pyrrolidinylcarbonyl)pyrazine

A mixture of 4 g (0.021 moles) of 3-Amino-2-(1-pyrrolidinylcarbonyl)pyrazine and 3.1 ml (0.023 moles) of N,N-dimethylformamide dimethylacetal in 11 ml of toluene was refluxed for 2 hours.
Evaporation in vacuo of the solvent and subsequent purification of the crude product by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/28% NH_4OH, 94:2:0.3 respectively, yielded 2.7 g of the title compound as an orange oil.

$C_{12}H_{17}N_5O$

M.W. = 247.296

Description 6

3-Hydroxyiminomethyleneamino-2-(1-pyrrolidinylcarbonyl)pyrazine

A solution of 1.46 g (0.021 moles) of hydroxylamine hydrochloride in 15 ml of MeOH was added dropwise, under mechanical stirring to a solution of 5 g (0.020 moles) of 3-dimethylaminomethyleneamino-2-(1-pyrrolidinylcarbonyl)pyrazine in 100 ml of MeOH containing 1.72 g (0.021 moles) of sodium acetate and kept at +5°C.
After 4 hours, the solution was evaporated in vacuo to dryness, the residue was taken up in CH_2Cl_2 and filtered. The filtrate was evaporated to dryness and the crude product purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/28% NH_4OH, 94:15:0.1 respectively, to yield 4.4 g of the title compound as yellow crystals.

$C_{10}H_{13}N_5O_2$

M.P. = 178-180°C
M.W. = 235.244

I.R. (KBr) : 3250; 1650; 1580; 1470 cm^{-1}
N.M.R. (80 MHz) $CDCl_3$: δ 10.90 (d,1H), 8.03-8.22 (m,4H), 3.65-4.00 (m,4H), 1.80-2.00 (m,4H).

Description 7

8-(1-Pyrrolidinylcarbonyl)-[1,2,4]triazolo[1,5-a]pyrazine

A mixture of 1.72 g (0.011 moles) of 3-hydroxyiminomethyleneamino-2-(1-pyrrolidinylcarbonyl)pyrazine and 17 g of polyphosphoric acid was heated at 90°C for 4 hours. The reaction mixture was therefore poured into ice/water and brought to pH = 8 with $NaHCO_3$. The acqueous layer was exhaustively extracted with methylene chloride and the organic solution was dried and evaporated in vacuo to dryness.
The crude product was purified by silica gel flash column chromatography, eluting with CH_2Cl_2/MeOH/28% NH_4OH, 94:3:0.3 respectively, to yield 1.3 g of the title compound as white crystals from ethyl acetate.

$C_{10}H_{11}N_5O$

M.P. = 123-125°C
M.W. = 217.228

I.R. (KBr) : 3090; 2885; 1650; 1485; 1310 cm^{-1}
N.M.R. (80 MHz) : δ 8.80 (d,1H), 8.52 (s,1H), 8.26 (d,1H), 3.80 (t,2H), 3.50 (t,2H), 1.80-2.05 (m,4H).
$CDCl_3$

Description 8

8- (1-Pyrrolidinylcarbonyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine

Prepared following Description n° 3, starting from 3.05 g (0.014 moles) of 8-(1-pyrrolidinylcarbonyl)-[1,2,4]triazolo[1,5-a]-pirazine. 2.9 g of the title compound were obtained and recrystallized from ethyl acetate.

$C_{10}H_{15}N_5O$

M.P. = 137-139°C
M.W. = 221.260

I.R. (KBr) : 3300; 2980; 1655; 1495; 1440 cm^{-1}
N.M.R. (80 MHz) : δ 7.85 (s,1H), 5.00 (s,1H), 4.00-4.30 (m,3H), 2.90-3.95 (m,5H), 2.50 (s broad,1H), 1.80-2.05 (m,4H).
$CDCl_3$

Description 9

8-(1-Pyrrolidinylmethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine

Prepared following Description n° 4, starting from 2.8 g of 8-(1-pyrrolidinylcarbonyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]-pyrazine.
2.5 g of the title compound were obtained as an oil and used in the subsequent reaction without further purification.

$C_{10}H_{17}N_5$

M.W. = 207.276

Example 1

7-[(3,4-Dichlorophenyl)acetyl]-8-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine

1 g (4.85 mmoles) of the compound of Description n° 4 was dissolved in 30 ml of dry methylene chloride and 0.66 g (4.86 mmoles) of anhydrous potassium carbonate were added.
1.2 g (5.36 mmoles) of (3,4-dichlorophenyl)acetyl chloride, dissolved in 10 ml of CH_2Cl_2, were added dropwise under magnetic stirring to the solution of the diamine.
After 3 hours the reaction mixture was allowed to reach room temperature and stirred overnight. 10 ml of water were added and the organic separated layer was dried over Na_2SO_4 and evaporated in vacuo to dryness.
The crude product was purified by silica gel flash column chromatography, eluting with CH_2Cl_2/MeOH/28% NH_4OH, 95:5:0.5 respectively, to yield 0.8 g of the title compound which was recrystallized from ethyl acetate / n-hexane.

$C_{19}H_{22}Cl_2N_4O$

M.P. = 78-80°C
M.W. = 393.312

Elemental analysis : Calcd C,58.02; H,5.64; N,14.25; Cl,18.03;
Found C,57.33; H,5.70; N,13.95; Cl,18.16.

I.R. (KBr) : 2980; 2800; 1635; 1615; 1470 cm^{-1}
N.M.R. (80 MHz) $CDCl_3$: δ 6.85-7.45 (m,5H), 4.50-5.80 (m,2H), 2.90-4.30 (m,7H), 2.30-2.80 (m,4H), 1.65-1.85 (m,4H).

Example 2

8-(1-Pyrrolidinylmethyl)-7-[(4-trifluoromethylphenyl)acetyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine

Prepared as described in Example n° 1, starting from 1 g (4.85 mmoles) of the compound of Description n° 4 and 1.2 g (5.40 mmoles) of (4-trifluoromethylphenyl)acetyl chloride in 30 ml of dry CH_2Cl_2.
Crystallization from ethyl acetate / n-hexane gave 0.7 g of the title compound as white crystals.

$C_{20}H_{23}F_3N_4O$

M.P. = 124-125°C
M.W. = 392.416

Elemental analysis : Calcd. C,61.21; H,5.91; N,14.28; F,14.52;
Found C,61.22; H,5.90; N,14.25; F,14.44.

I.R. (KBr) : 2960; 2790; 1650; 1490; 1415; 1320 cm^{-1}
N.M.R. (80 MHz) $CDCl_3$: δ 7.25-7.60 (m,4H), 7.05 (d,1H), 6.82 (d,1H), 4.50-5.90 (m,2H), 3.20-4.20 (m,5H), 3.00-3.15 (m,2H), 2.20-2.80 (m,4H), 1.55-1.85 (m,4H).

Example 3

7-[(3,4-Dichlorophenyl)acetyl]-8-[(3-hydroxy-1-pyrrolidinyl)-methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine diastereomeric mixture.

Prepared as described in Example n° 1, starting from 0.8 g (3.60 mmoles) of 8-[(3-hydroxy-1-pyrrolidinyl)methyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine diastereomeric mixture and 0.96 g (4.32 mmoles) of (3,4-dichlorophenyl)acetyl chloride in 20 ml of dry DMF.
The crude product was purified by silica gel flash column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/28% NH_4OH, 86:10:0.6 respectively, to yield 0.4 g of the title compound which was recrystallized from ethyl acetate.

$C_{19}H_{22}Cl_2N_4O_2$

M.P. = 160-175°C
M.W. = 409.312

Elemental analysis: Calcd. C,55.75; H,5.42; N,13.69; Cl,17.32;
Found C,55.09; H,5.40; N,13.49; Cl,18.03.

I.R. (KBr) : 3250; 2920; 2790; 1650; 1435 cm^{-1}
N.M.R. (80 MHz) : δ 6.75-7.45 (m,5H), 4.50.5.80 (m,2H), 3.30-
$CDCl_3$ 4.40 (m,5H), 1.50-3.30 (m,10H).

Example 4

7-[(3,4-Dichlorophenyl)acetyl]-8-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine.

Prepared as described in Example n° 1, starting from 1.5 g (7.24 mmoles) of the compound of Description n° 9 and 1.86 g (8.32 mmoles) of (3,4-dichlorophenyl)acetyl chloride in 50 ml of dry CH_2Cl_2.

The crude product was purified by silica gel flash column chromatography, eluting with CH_2Cl_2/MeOH/28% NH_4OH, 86:12:0.6 respectively, to yield 1.0 g of the title compound.

$C_{18}H_{21}Cl_2N_5O$

M.P. = 113-116°C
M.W. = 394.302

Elemental analysis : Calcd. C,54.83; H,5.37; N,17.76; Cl,17.98;
Found C,54.69; H,5.34; N,17.71; Cl,18.07.

I.R. (KBr) : 2980; 2790; 1645; 1400 cm^{-1}
N.M.R. (80 MHz) $CDCl_3$: δ 7.90 (s,1H), 7.00-7.45 (m,3H), 4.60-6.10 (m broad,1H), 3.40-4.50 (m,6H), 2.90-3.35 (m,2H), 2.10-2.90 (m,4H), 1.40-2.00 (m,4H).

Example 5

8-(1-Pyrrolidinylmethyl)-7-[(4-trifluoromethylphenyl)acetyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine dihydrochloride

Prepared as described in Example n° 1, from 1.5 g (7.24 mmoles) of the compound of Description n° 9 and 1.85 g (8.32 mmoles) of (4-trifluoromethylphenyl)acetyl chloride in 50 ml of dry CH_2Cl_2. The crude product was purified by silica gel flash column chromatography, eluting with CH_2Cl_2/MeOH/28% NH_4OH, 86:15:0.7 respectively, to yield 1.2 g of the pure free base which was transformed into the dihydrochloride salt recrystallized from EtOAc/acetone.

$C_{19}H_{22}F_3N_5O \cdot 2HCl$

M.P. = 176-177°C
M.W. = 466.336

Elemental analysis: Calcd. C,48.93; H,5.19; N,15.02; Cl,15.21; F,12.22;
Found C,48.22; H,5.19; N,14.69; Cl,15.09. F,11.86.

I.R. (KBr) : 3420; 2560; 1660; 1330 cm^{-1}
N.M.R. (80 MHz) $CDCl_3$+NaOD : δ 7.90 (s,1H); 7.25-7.70 (m,4H); 4.60-6.10 (m broad,1H); 3.50-4.50 (m,6H); 2.90-3.15 (m,2H); 2.20-2.70 (m,4H); 1.50-1.90 (m,4H).

The following compounds may be prepared in a similar manner to those of Examples 1 to 5:

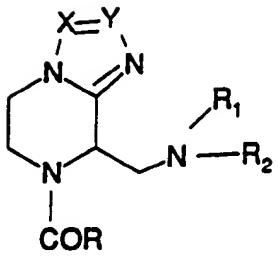
7-[(3,4-Dichlorophenyl)acetyl]-8-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine

8-(1-Pyrrolidinylmethyl)-7-[(4-trifluoromethylphenyl)acetyl]-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine

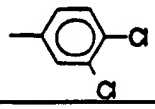
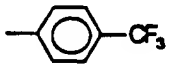
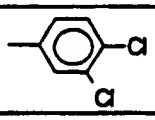
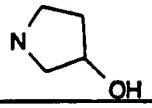
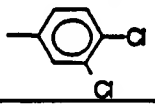
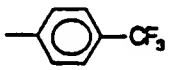
7-[(3,4-Dichlorophenyl)acetyl]-8-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyrazine

8-(1-Pyrrolidinylmethyl)-7-[(4-trifluoromethylphenyl)acetyl]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyrazine

TABLE

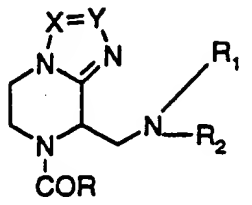


(I)

Example No.	X	Y	R	NR_1R_2	MOLECULAR FORMULA	M.P. (°C)
1	CH	CH			$C_{19}H_{22}Cl_2N_4O$	78-80
2	CH	CH			$C_{20}H_{23}F_3N_4O$	124-125
3 DIAST. MIX	CH	CH			$C_{19}H_{22}Cl_2N_4O_2$	160-175
4	N	CH			$C_{18}H_{21}Cl_2N_5O$	113-116
5	N	CH			$C_{19}H_{22}F_3N_5O.$ 2HCl	176-177

CLAIMS

1. A compound, or a solvate or salt thereof, of formula (I):



(I)

in which:

each of X and Y is independently CH or N;

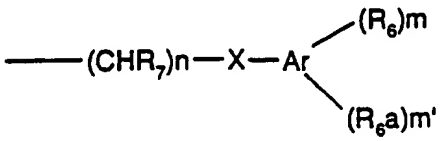
RCO is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

each of R_1 and R_2, which may be the same or different, is C_{1-6} alkyl optionally substituted by at least one of halogen, hydroxy, C_{1-6} alkoxy, acyloxy, thiol, C_{1-6} alkylthio, acylthio, halo-C_{1-6} alkoxy, COR_h, $COOR_h$, $CONHR_h$ or $NCHOR_h$ where R_h is hydrogen or C_{1-6} alkyl;

or each of R_1 and R_2 is hydrogen, C_{2-6} alkenyl, C_{3-6} cycloalkyl, or C_{4-12} cycloalkylalkyl;
or R_1 and R_2 together form an optionally substituted C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group.

2. A compound according to claim 1, in which R contains a single or fused carbocyclic ring having 6 to 12 ring carbon atoms, or a single or fused heterocyclic ring having 5 to 12 ring atoms, the heterocyclic ring comprising up to four hetero-atoms in the or each ring, selected from oxygen, nitrogen and sulphur.

3. A compound according to claim 1 or 2, in which R has the formula (II)



(II)

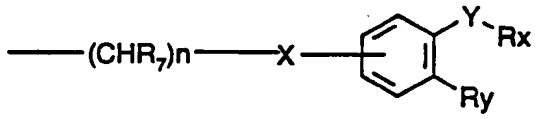
in which n is 0, 1 or 2:

m is 0, 1 or 2;
m' is 0, 1 or 2, provided m + m'≤3
X is a direct bond, or O, S or NR_8 in which

R_8 is hydrogen or C_{1-6} alkyl,
Ar is a substituted or unsubstituted carbocyclic or heterocyclic group,

each of R_6 and R_6a is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6}haloalkenyl, C_{2-6} haloalkynyl, optionally substituted phenyl or heterocyclyl, optionally substituted phenyl C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, thiol, C_{1-6} alkylthio, C_{1-6} haloalkoxy, C_{1-6} haloalkylthio, halogen, NO_2, CN, CF_3, $-OCF_3$, $-OCHF_2$, $-OCF_2CF_2H$, $-OCCl_2CF_3$, $-COOR_9$, $-CONR_{10}R_{11}$, $-SO_3R_{12}$, $-SONR_{13}R_{14}$ and $-COR_{15}$ in which each of R_9 to R_{15} is independently hydrogen, C_{1-6} alkyl, optionally substituted phenyl or optionally substituted phenyl C_{1-6} alkyl;
or, when m is 2 and m' is O, two R_6's form a C_{3-6} polymethylene group, and R_7 is hydrogen or C_{1-6} alkyl.

4. A compound according to claim 1 or 2, in which R hs the formula (IIa).



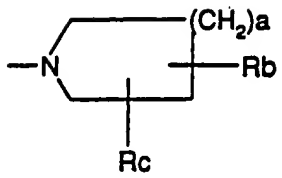
(IIa)

in which the group $-(CHR_7)_n-X-$, which is as defined in formula II in claim 3 is in the meta- or para- position with respect to YR_x or R_y,

Y is >C=O, >CHOH, >S=O or $>SO_2$;
each of R_x and R_y is C_{1-6} alkyl, or
R_x and R_y are linked together and R_x represents $-(Z_m)-$
where m is 0 or 1 and Z is O, S or NR_z where R_z is hydrogen or C_{1-6} alkyl,
and R_y represents $-(CH_2)q-$ where q is an integer of from 1 to 4.

5. A compound according to claim 1 or 2 in which R is benzyl substituted by dichloro or trifluoromethyl.

6. A compound according to any one of claims 1 to 5 in which R_1 and R_2 together form a group



in which Rb, which may be attached to the same or different carbon atom as Rc, is hydrogen, hydroxy, C_{1-6} alkoxy or halogen,
Rc is hydrogen or C_{1-6} alkyl,
and a is 1 or 2.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 6 for use as an active therapeutic substance.

9. A compound according to any one of claims 1 to 6 for use in the treatment of pain, convulsions, cough, asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states, cerebral ischaemia or skin disorders.

10. The use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment of pain, convulsions, cough, asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states, cerebral ischaemia or skin disorders.

11. A method for the treatment and/or prophylaxis of pain, convulsions, cough, asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states, cerebral ischaemia or skin disorders in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound according to any one of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

Int .onal Application No
PCT/EP 95/00345

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 366 327 (GLAXO) 2 May 1990 see page 6, line 4-32; claim 1	1,9
A	EP,A,0 330 469 (GLAXO) 30 August 1989 see page 1, line 6-8; claim 1	1,9
A	EP,A,0 398 720 (GLAXO) 22 November 1990 cited in the application see page 1, line 1-34; claim 1	1,9
A	EP,A,0 343 900 (GLAXO) 29 November 1989 cited in the application see page 1, line 1-19; claim 1	1,9
A	EP,A,0 356 247 (SANKYO) 28 February 1990 cited in the application see page 1, line 5-26; claim 1	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 May 1995	06.06.95

Name and mailing address of the ISA	Authorized officer
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